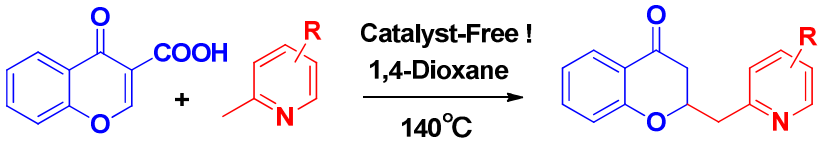
RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances



A facile catalyst-free tandem sp3 C–H functionlization/ decarboxylation of 4-oxo-4H-chromene-3-carboxylic acid with 2-alkylazaarenes was developed, which can efficiently construct azaarene 2-substituted chromanones in moderate to good yields. This method proves to be efficient and innovative and the biologically significant azaarene 2-substituted chromanones can be accessed in a single step through this methodology.

Journal Name

RSCPublishing

COMMUNICATION

Facile synthesis of azaarene-2-substituted chromanone derivatives via tandem sp^3 C−H functionlization/ decarboxylation of azaarenes with 4-oxo-4H-chromene-3-carboxylic acid

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Zhuzhou Shao, Liang Wang, Lubin Xu, Huaili Zhao and Jian Xiao*

A facile catalyst-free tandem sp^3 C−H functionlization/ decarboxylation of 4-oxo-4H-chromene-3-carboxylic acid with 2-alkylazaarenes was developed, which can efficiently construct azaarene 2-substituted chromanones in moderate to good yields. This method proves to be efficient and innovative and the biologically significant azaarene 2-substituted chromanones can be accessed in a single step through this methodology.

Over the past years, the concept of privileged skeleton has arisen and played important role in drug discovery and development. There is no dispute that chromanone is such a scaffold which represents an important class of naturally occurring structures, characterized by their abilities to interact with a number of different receptors in the body,[1] e.g. Taxifolin (Antibacterial),[1g] 12-Oxocalanolide A (Anti-HIV-1),[2] Aposphaerin A (Antibacterial),[1i] Gonytolide A (Innate immune promoter) (Figure 1).[1f,1h,3] Due to their attractive pharmacological and biological properties, great efforts have been devoted to the development of efficient synthetic approaches to access this class of privileged compounds during the past decades.[4]

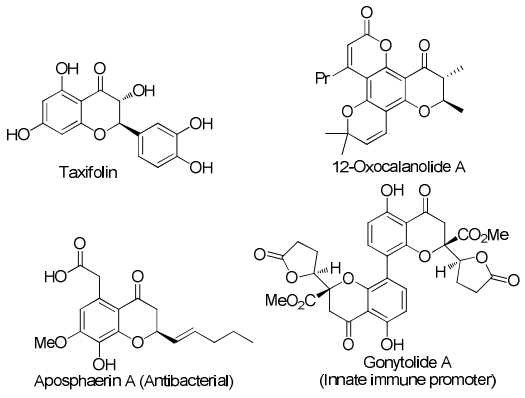


Figure 1. Several natural products with chromanone as the structural scaffold

Intramolecular Stetter reaction has been demonstrated to be a powerful strategy for the synthesis of 3-substituted chromanones,[4d-h] while 2-substituted chromanones can be facilely accessed *via* 1,4-conjugate addition of various nucleophiles to chromones.[1d, 4c, 5] This structure can also be readily furnished *via* alkyltin-free radical methodology[6] or intramolecular oxa-Michael cyclization of substituted 2-hydroxy-chromones prepared *in situ*[1c, 7] or beforehand.[3, 8] Remarkably, Photo-Fries rearrangement has also been exploited to prepare chromanones from readily available (hetero)aryl 3-methyl-2-butenoate esters.[9] Fused or spiro chromanones can also be facilely constructed through the direct oxidative coupling,[10] 1,3-dipolar cycloaddition,[11] Diels-Alder reaction,[12] etc.

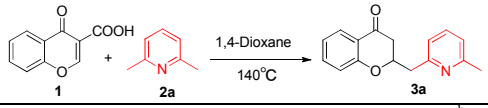
The azaarene unit is an extremely important pharmacophore which exists in many natural and synthetic bioactive compounds.[13] Owing to the high significance of azaarenes and chromanones, it is of vital importance to modify and functionalize these two class of compounds from the viewpoints of both organic and medicinal chemists. However, to the best of our knowledge, no direct method is available to prepare this novel and biologically important azaarene-2-substituted chromanones despite their potential to be new biologically important compounds and new pharmaceuticals.

Substituted azaarene derivatives can be readily accessed *via* activation of 2-alkylazaarenes catalyzed by a variety of transition metals, such as scandium,[14] copper,[15] palladium,[16] iron[17] and ytterbium.[18] Recently, significant progresses have been achieved for direct sp^3 C−H functionalization of 2-alkylazaarenes without resorting to the toxic transition metals.[19,20] As a continuation of development of efficient and green methodology to construct biologically and pharmaceutically important molecules,[20] herein we report a catalyst-free tandem sp^3 C−H activation/decarboxylation of 2-alkylazaarenes with 4-oxo-4H-chromene-3-carboxylic acids which

furnished the azaarene 2-substituted chromanone derivatives in one step (Scheme 1c).

From our previous work,[20b] we have learned that carboxylic group introduced into electron-deficient olefins can serve as Brønsted acids for activation of 2-alkylazaarenes, triggering the reaction in the absence of catalyst. As a further research of this chemistry, 4-oxo-4H-chromene-3-carboxylic acid was selected as the substrate to undertake this tandem reaction, aiming to construct azaarene 2-substituted chromanone derivatives in one step. To validate our proposal, the initial investigation was conducted via the reaction of 4-oxo-4H-chromene-3-carboxylic acid **1** and 2,6-lutidine **2a** under catalyst-free condition in dioxane at 140 ℃ (Table 1, entry 5). Gratifyingly, the reaction proceeded successfully and the coupled product **3a** was obtained in 67% yield. Notably, only one methyl of 2,6-lutidne was functionalized, which might be rationalized that the second functionalization of **3a** was blocked because of the increased steric hindrance in 3a. The employment of other solvents only led to inferior yields (Table 1, entries 1−4). Afterwards, a variety of Lewis acids and Brønsted acids (10 mol%) were examined at 140 ℃ for comparison with the catalyst-free condition. It was intriguing to find that almost all the tested Lewis acids and Brønsted acids, such as Sc(OTf)3, $La(OTf)_3$, AgOTf, TfOH, HOAc (Table 1, entries 6-9,11), gave inferior yields except TFA (Table 1, entry 10), which were in sharp contrast with the effective sp^3 C−H activation reaction catalyzed by Lewis and Brønsted acids.[14a,14b,20a] Thus our hypothesis was eventually corroborated.

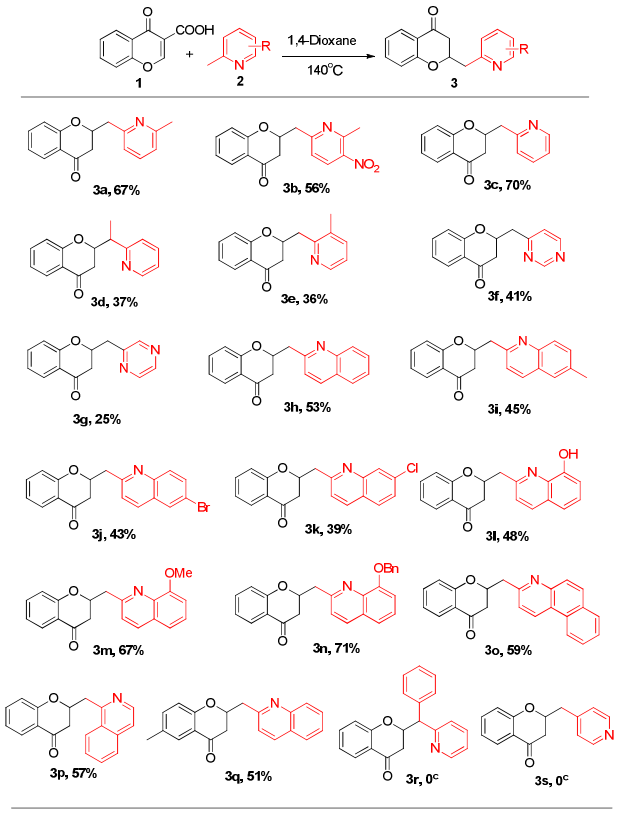
Table 1 Optimization of Reaction Conditions [a]



Entry	Solvent	Catalyst	Yield(%)[b]
1	DMF	-	38
2	THF	-	39
3	Toluene	-	35
4	DCE	-	26
5	1,4-Dioxane	-	67
6	1,4-Dioxane	$Sc(OTf)_3$	Trace
7	1,4-Dioxane	$La(OTf)_3$	16
8	1,4-Dioxane	AgOTf	65
9	1,4-Dioxane	TfOH	23
10	1,4-Dioxane	TFA	70
11	1,4-Dioxane	AcOH	Trace

[a] Reaction were conducted with 1 (0.3 mmol), 2a (0.75 mmol) in 2 mL solvent at 140 ℃ for 48h [b] The yields indicated are the isolated yield by column chromatography.

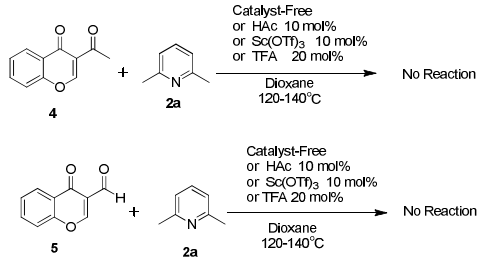
Subsequently the substrate scope was investigated and the results are shown in Scheme 2. A series of electronically and sterically diverse 2-alkyl substituted azaarenes were tolerated under the optimized condition. The position of alkyl group was critical to the success of this tandem process. For example, the methyl of 2-methyl pyridine and 3-nitro-2,6-lutidine could be smoothly functionalized (**3b**, **3c**); whereas the 3-methyl or 4-methyl on pyridine substrates could not be tolerated in this reaction (**3e** and **3r**). The steric hindrance dramatically influenced the yields of the products such as yields of **3d**, **3e** were decreased when compared with 2-methylpyridine (**3c**) and product (**3q**) was not determined. Notably, free OH group can be tolerated in this reaction (**3l**). The electron-donating groups such as OMe and OBn were beneficial to this reaction (**3m**, **3n**). However, when nitro group was introduced to *para*-position of 2,6-lutidine, the yield was decreased to 56% (**3b**), which might be ascribed to electron-deficiency caused by nitro group. Additionally, 2-methylquinoline (**3h**), 1-methylisoquinoline (**3p**), 2,6-dimethylquinoline (**3i**) and 6-bromo-2-methylquinoline (**3j**) were also well-tolerated to produce the analogous coupled products in moderate to good yields. Moreover, the methyl of 4-methylpyrimidine (**3f**) and 2-methylpyrazine (**3g**) could also be functionalized. As to **3j** and **3k**, the bromo- and chloro-substituents are versatile synthetic handles which can be further elaborated in miscellaneous means, e.g. transition metal catalyzed couple reaction and lithium-halogen exchange reaction. Other 4-oxo-4H-chromene-3-carboxylic acids such as 6-methyl-4-oxo-4H-chromene-3-carboxylic acid can also work for this reaction to give product **3q** in 51% yield.



[a] Reactions were conducted with 1 (0.3 mmol), 2a (0.75 mmol) in 1,4-dioxane (2 mL) at 140 ℃ for 48h; [b] The yields indicated are the isolated yield by column chromatography; [c] 20 mol% TFA or 20 mol% AgOTf

Scheme 2. Substrate scope.

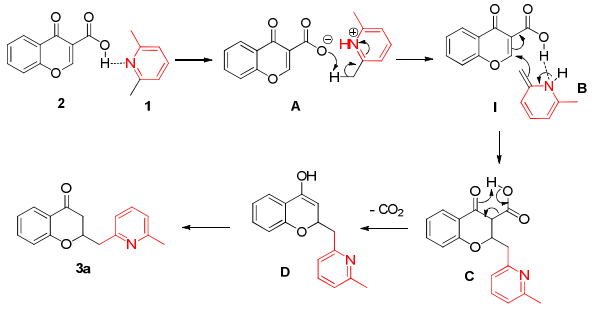
To explicate the reaction mechanism, 3-acetyl-4H-chromen-4-one **4** and 4-oxo-4H-chromene-3-carbaldehyde **5** were prepared and subjected to the optimized condition (Scheme 3). Despite the fact that the acetyl and formyl group are electron-withdrawing groups which can make the alkene more electrophilic, both of them remained intact under the standard reaction condition. No reaction occurred even in the presence of AcOH (10 mol%), $Sc(OTf)_3$ (10 mol%), or TFA (20 mol%). These results strongly indicated that the presence of carboxylic group connected to the alkene at C-3 position was crucial



Scheme 3. Control Experiments

and irreplaceable for this tandem process. Presumably, the carboxyl group in C-3 position of 4-oxo-4H-chromene-3-carboxylic acid 1 can not only render the alkene electron deficient, but also bring the 2-alkyl-azaarene closer to the Michael acceptor by hydrogen bonding.

On the basis of the above-mentioned reactions, the proposed mechanism is outlined in Scheme 4. Basically, 4-oxo-4H-chromene-3-carboxylic acid **1** and 2-methylazaarenes **2** aggregate together via hydrogen-bonding interaction, followed by protonation of 2-methylazaarene **1** to give pyridinium A. As a result of the enhanced acidity of the benzylic proton, the cleavage of benzylic C-H bond ensues to afford enamine intermediate B, which attacks the electron-deficient alkene of **1** *via* the well-organized transition state I, giving rise to the intermediate **D**. In the transition state **C**, hydrogen-bonding interaction between intermediate **B** and 4-oxo-4H-chromene-3-carboxylic acid **1** helps the nucleophilic enamine B to approach electrophilic alkene moiety. The subsequent decarboxylation and isomerization of intermediate **D** leads to the final product 3a. The overall result of this tandem process is that the comparatively inert benzylic sp^3 C-H bond is activated and directly functionalized. In the whole process, hydrogen bonding plays a key role for the success of this transformation.



Scheme 4. Proposed reaction mechanism.

Conclusions

In summary, a facile catalyst-free tandem sp3 C−H functionlization/decarboxylation of 4-oxo-4H-chromene-3-carboxylic acid with 2-alkylazaarenes was developed, which efficiently constructed biologically significant azaarene 2-substituted chromanone derivatives in one step. A variety of electronically and sterically diverse azaarenes were well tolerated, and the coupled products were isolated in moderate to good yields. This method proves to be efficient and innovative, which broaden the library of chromanones in pharmaceutical chemistry and extend the synthetic utility of sp^3 C−H functionalization in organic synthesis.

Acknowledgement. We are grateful to the National Natural Science Foundation of China (No. 21102142) and the Outstanding Young Scientist Award Foundation of Shandong Province (No. BS2011YY007, BS2013YY002) and Qingdao Special Research Foundation of Science and Technology (14-2-4-70-jch). Financial supports from Talents of High Level Scientific Research Foundation (No. 631223) of Qingdao Agricultural University is also gratefully acknowledged.

Notes and references

College of Chemistry and Pharmaceutical Sciences, Qingdao Agricultural University, Qingdao, 266109, China.
E-mail: chemjianxiao@gmail.com

† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1. (a) F. Cottiglia, B. Dhanapal, O. Sticher and J. Heilmann, *J. Nat. Prod.*, 2004, **67**, 537; (b) X. Yang, Y. Sun, Q. Xu and Z. Guo, *Org. Biomol. Chem.*, 2006, **4**, 2483; (c) P. L. Zhao, J. Li and G. F. Yang, *Bioorg. Med. Chem.*, 2007, **15**, 1888; (d) N. Hoettecke, S. Rotzoll, U. Albrecht, M. Lalk, C. Fischer and P. Langer, *Bioorg. Med. Chem.*, 2008, **16**, 10319; (e) P. Y. Chen, Y. C. Kuo, C. H. Chen, Y. H. Kuo and C. K. Lee, *Molecules*, 2009, **14**, 1789; (f) H. Kikuchi, M. Isobe, M. Sekiya, Y. Abe, T. Hoshikawa, K. Ueda, S. Kurata, Y. Katou and Y. Oshima, *Org. Lett.*, 2011, **13**, 4624; (g) X. Wu, M. Z. Alam, L. Feng, L. S. Tsutsumi, D. Sun and J. G. Hurdle, *J. App. Microbiol.*, 2014, **116**, 23; (h) L. F. Tietze, S. Jackenkroll, J. Hierold, L. Ma and B. Waldecker, *Chem. Eur. J.*, 2014, **20**, 8628; (i) P. N. Moquist, T. Kodama and S. E. Schaus, *Angew. Chem. Int. Ed.*, 2010, **49**, 7096.
2. Z.-Q. Xu, J. Robert W. Buckheit, T. L. Stup, M. T. Flavin, A. Khilevich, J. D. Rizzo, L. Lin and D. E. Zembower, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2179.
3. G. Sudhakar, S. Bayya, V. D. Kadam and J. B. Nanubolu, *Org. Biomol. Chem.*, 2014, **12**, 5601.
4. (a) N. X. Wang, Y. Xing and Y. J. Wang, *Curr. Org. Chem.*, 2013, **17**, 1555; (b) A. E. Nibbs and K. A. Scheidt, *Eur. J. Org. Chem.*, 2012, 449; (c) L. A. Stubbing, F. F. Li, D. P. Furkert, V. E. Caprio and M. A. Brimble, *Tetrahedron*, 2012, **68**, 6948; (d) D. Enders, K. Breuer and J. Runsink, *Helv. Chim. Acta*, 1996, **79**, 1899; (e) J. R. d. Alaniz and T. Rovis, *J. Am. chem. Soc.*, 2005, **127**, 6284; (f) L. R. Domingo, R. J. Zaragoza, J. A. Saez and M. Arno, *Molecules*, 2012, **17**, 1335; (g) J. He, J. Zheng, J. Liu, X. She and X. Pan, *Org. Lett.*, 2006, **8**, 4637; (h) S.-L. You, Z.-Q. Rong, Y. Li and G.-Q. Yang, *Synlett*, 2011, **2011**, 1033-1037; (i) A. Gaspar, M. J. Matos, J. Garrido, E. Uriarte and F. Borges, *Chem. Rev.*, 2014, **114**, 4960.
5. (a) C. Vila, V. Hornillos, M. Fañanás-Mastral and B. L. Feringa, *Chem. Commun.*, 2013, **49**, 5933; (b) M. K. Brown, S. J. Degrado and A. H. Hoveyda, *Angew. Chem. Int. Ed.*, 2005, **44**, 5306; (c) Ö. Z. Sirin, O. Demirkol, D. Akbaslar and E. S. Giray, *J. Supercritical Fluids*, 2013, **81**, 217; (d) B. Appel, N. N. Saleh and P. Langer, *Chem. Eur. J.*, 2006, **12**, 1221; (e) S. J. Coutts and T. W. Wallace, *Tetrahedron Lett.*, 1987, **28**, 5195.
6. (a) J. R. Zimmerman, M. Manpadi and R. Spatney, *Green Chem.*, 2011, **13**, 3103; (b) Y.-J. Jang, M.-C. Yan, Y.-F. Lin and C.-F. Yao, *J. Org. Chem.*, 2004, **69**, 3961.
7. (a) Y. Wei, J. Tang, X. Cong and X. Zeng, *Green Chem.*, 2013, **15**, 3165; (b) C.-H. Tseng, R.-W. Lin, Y.-L. Chen, G.-J. Wang, M.-L. Ho and C.-C. Tzeng, *J. Med. Chem.*, 2011, **54**, 3103.
8. (a) M. M. Biddle, M. Lin and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 3830; (b) A. K. Ghosh, X. Cheng and B. Zhou, *Org. Lett.*, 2012, **14**, 5046.
9. C. S. López, R. Erra-Balsells and S. M. Bonesi, *Tetrahedron Lett.*, 2010, **51**, 4387.

10.E. Jijy, P. Prakash, M. Shimi, P. M. Pihko, N. Joseph and K. V. Radhakrishnan, *Chem. Commun.*, 2013, **49**, 7349.
11. T.-L. Liu, Z.-L. He and C.-J. Wang, *Chem. Commun.*, 2011, **47**, 9600.
12.Z. Mao, A. Lin, Y. Shi, H. Mao, W. Li, Y. Cheng and C. Zhu, *J. Org. Chem.*, 2013, **78**, 10233.
13. (a) M. C. Bagley, C. Glover and E. A. Merritt, *Synlett*, 2007, 2459; (b) G. D. Henry, *Tetrahedron*, 2004, **60**, 6043; (c) J. P. Michael, *Nat. Prod. Rep.*, 2005, **22**, 627.
14. (a) B. Qian, S. Guo, C. Xia and H. Huang, *Adv. Synth. Catal.*, 2010, **352**, 3195; (b) H. Komai, T. Yoshino, S. Matsunaga and M. Kanai, *Org. Lett.*, 2011, **13**, 1706; (c) M. Kanai, S. Matsunaga, H. Komai and T. Yoshino, *Synthesis*, 2012, **44**, 2185-2194.
15. (a) J.-J. Jin, H.-Y. Niu, G.-R. Qu, H.-M. Guo and J. S. Fossey, *RSC Adv.*, 2012, **2**, 5968; (b) M. Rueping and N. Tolstoluzhsky, *Org. Lett.*, 2011, **13**, 1095; (c) F.-F. Wang, C.-P. Luo, G. Deng and L. Yang, *Green Chem.*, 2014, **16**, 2428; (d) Z. Q. Zhu, P. Bai and Z. Z. Huang, *Org. Lett.*, 2014, DOI: dx.doi.org/10.1021/ol502402s.
16. (a) J. Y. Liu, H. Y. Niu, S. Wu, G. R. Qu and H. M. Guo, *Chem. Commun.*, 2012, **48**, 9723; (b) B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia and H. Huang, *J. Am. Chem. Soc.*, 2010, **132**, 3650.
17. (a) S. J. Lou, D. Q. Xu, D. F. Shen, Y. F. Wang, Y. K. Liu and Z. Y. Xu, *Chem. Commun.*, 2012, **48**, 11993; (b) P. X. Qian, Y. Xie and H. Huang, *Org. Lett.*, 2011, **13**, 2580; (c) Y. Li, F. Guo, Z. Zha and Z. Wang, *Chem. Asian. J.*, 2013, **8**, 534.
18. (a) R. Niu, S. Yang, J. Xiao, T. Liang and X. Li, *Chin. J. Catal.*, 2012, **33**, 1636; (b) V. B. Graves and A. Shaikh, *Tetrahedron Lett.*, 2013, **54**, 695.
19. (a) F. F. Wang, C. P. Luo, Y. Wang, G. Deng and L. Yang, *Org. Biomol. Chem.*, 2012, **10**, 8605; (b) S. V. N. Vuppalapati and Y. R. Lee, *Tetrahedron*, 2012, **68**, 8286; (c) A. Kumar, L. P. Gupta and M. Kumar, *RSC Advances*, 2013, **3**, 18771; (d) H.-Y. Li, L.-J. Xing, T. Xu, P. Wang, R.-H. Liu and B. Wang, *Tetrahedron Lett.*, 2013, **54**, 858; (e) H. M. Meshram, N. Nageswara Rao, L. Chandrasekhara Rao and N. Satish Kumar, *Tetrahedron Lett.*, 2012, **53**, 3963; (f) K. Kumari, B. K. Allam and K. N. Singh, *RSC Advances*, 2014, **4**, 19789; (g) M. Raghu, M. Rajasekhar, B. Chandra Obula Reddy, C. Suresh Reddy and B. V. Subba Reddy, *Tetrahedron Lett.*, 2013, **54**, 3503; (h) X. Gao, F. Zhang, G. Deng and L. Yang, *Org. Lett.*, 2014, **16**, 3664.
20. (a) R. Niu, J. Xiao, T. Liang and X. Li, *Org. Lett.*, 2012, **14**, 676; (b) L. Xu, Z. Shao, L. Wang and J. Xiao, *Org. Lett.*, 2014, **16**, 796; (c) Z. Shao, L. Xu, L. Wang, H. Wei and J. Xiao, *Org. Biomol. Chem.*, 2014, **12**, 2185; (d) J. Xiao, K. Zhao and T. P. Loh, *Chem. Commun.*, 2012, **48**, 3548; (e) T. Liang, J. Xiao, Z. Xiong and X. Li, *J. Org. Chem.*, 2012, **77**, 3583; (f) X. Yu, S. Yu, J. Xiao, B. Wan and X. Li, *J. Org. Chem.*, 2013, **78**, 5444; (g) X. Li, Y. Jiang, X. Wang, X. Li and J. Xiao, *Synlett*, 2012, **23**, 1649-1652; (h) J. Xiao, Y. Chen, S. Zhu, L. Wang, L. Xu and H. Wei, *Adv. Synth. Catal.*, 2014, **356**, 1835-1845; (i) L. Wang, J. Xiao and T.-P. Loh, *ChemCatChem*, 2014, **6**, 1183; (j) F. Huang, L. Xu and J. Xiao, *Chin. J. Chem.* , 2012, **30**, 2721.

